

The amendments to claim 12 are supported, for example, by Example 3 of the specification.

The amendments to claim 18 are supported, for example, by the specification at page 7, lines 5-11.

The amendments to claim 19 are supported, for example, by the specification at page 7, lines 17-21.

The amendments to claim 20 are supported, for example, by the specification at page 7, lines 5-28.

The amendments to claim 21 are supported, for example, by the specification at page 7, lines 5-28.

New claim 22 is supported, for example, by the specification at page 2, lines 26-30.

I. The 35 U.S.C. § 112 Second Paragraph Rejections of the Claims

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The Examiner rejected claims 6-8, 11-12, 18-19 and 21 under 35 U.S.C. § 112, second paragraph, alleging that those claims are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A. Claims 6-8

The Examiner rejected claims 6-8, alleging that the limitation "claim 11" in the first line of these claims lacks antecedent basis. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Claim 11 is directed to a process for the production of a *Haemophilus influenzae*-specific lipooligosaccharide. Claims 6-8 depend directly or indirectly from claim 11. Claim 6 has been amended to recite the process of claim 12, wherein the bacteria are *Escherichia coli* K-12 strain JM 109. (Claim 12 recites the process of claim 11, wherein the bacteria are *Escherichia coli*.) Claim 7 recites the process of claim 11, wherein the acceptor molecule is N-acetylglucosamine. Claim 8 recites the process of claim 11, wherein the *rfe* gene is from *Haemophilus influenzae*. Claim 11 is directed to a process, and the language in the preamble of claims 6-8 indicates that those claims depend from claim 11. Thus, claims 6-8 are not indefinite. Therefore, Applicant requests that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejection of claims

6-8.

Applicant acknowledges that due to amendments made to the claims, claims 6-8 depend from a subsequent independent claim. As required by M.P.E.P. § 608.01(j) "[t]he original numbering of the claims must be preserved throughout the prosecution. . . . [w]hen the application is ready for allowance, the examiner, if necessary, will renumber the claims consecutively in the order in which they appear or in such order as may have been requested by applicant." Applicant presumes that the Examiner will renumber the claims upon allowance, such that original claim 11 will become issued claim 1, and that claims 6-8 will be appropriately re-numbered as subsequent claims.

B. Claims 11-12, 18-19 and 21

The Examiner rejected claims 11-12, 18-19 and 21, alleging that the phrase "DNA sequence encoding a lipooligosaccharide-synthesis gene (*lsg*)" is confusing. Claims 8, 11, 18, 19, 20 and 21 have been amended to clarify the relationship between the DNA sequences and the proteins that are encoded by the DNA sequences. Applicant requests that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejection of claims 11-12, 18-19 and 21.

C. Conclusion

It is respectfully submitted that the pending claims conform with 35 U.S.C. § 112, second paragraph. Therefore, Applicant requests that the Examiner withdraw the 35 U.S.C. § 112, second paragraph rejections.

II. The 35 U.S.C. § 112 First Paragraph Rejections of the Claims

A. The Written Description Rejection

The Examiner rejected claims 8, 11-12 and 20-21 under 35 U.S.C. § 112, first paragraph, alleging that those claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleges that while the specification discloses an *rfe* gene from *E. coli*, it does not describe *rfe* genes from "any" source. According to the Examiner, as "only one representative species of a diverse genus" is described, the specification fails to sufficiently describe the claimed invention.

As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

As an initial matter, Applicant respectfully notes that the Examiner, at page 3 of the Office Action, alleges that the *E. coli* used in the working examples in the specification were transformed with *rfe*. However, the Examiner is respectfully reminded that the *E. coli* used in the working examples were not transformed with *rfe*. As is indicated at page 8, lines 6-14 of the specification, bacteria useful as production cells may contain an enzyme capable of adding an acceptor molecule to the terminal molecule to serve as a scaffold, and cells that are otherwise suitable can be co-transformed with genes such as *rfe* and *lsgG*. Thus, in some embodiments of Applicant's invention, it is appropriate to transform production cells that lack the appropriate enzyme with a DNA sequence comprising an *rfe* gene, for example, with the *rfe* gene from *H. influenzae*. However, transformation of the *E. coli* with an *rfe* gene was not necessary because the *E. coli* already contained the *rfe*.

Additionally, the Examiner alleges that "art nor the specification describe a *rfe* from *H. influenzae* to use in the claimed method." (page 3 of the Office Action) However, the specification discloses at page 4, line 29 through page 5, line 1, that an *rfe* gene from *H. influenzae* may be used. At page 6, lines 6-8, it is disclosed that the nucleotide sequence for a *H. influenzae rfe* is available in the TIGR database. (The Primary Accession Number is P45341. The annotations indicate that the sequence was last modified November, 1995.) Therefore, an *rfe* from *H. influenzae* was available to the art worker at the time the application was filed.

To satisfy the written description requirement, an Applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was legally in possession of the elements of the invention sought to be patented, i.e., whatever is claimed. M.P.E.P. §2163; *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997); *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991).

A patent application need not teach, and preferably omits, what is well known in the art. "Guides for Examination of Patent Applications under the 35 U.S.C. § 112, ¶ 1 'Written Description' Requirement," 66 *Fed Reg* 1099, 1105 (2001). (The absence of definitions or

details for well-established terms should not be the basis for rejection for lack of adequate written description); *Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987). In other words, the sufficiency of the specification must be evaluated from the viewpoint of one skilled in the art, who is also in possession of all of the relevant prior art. Thus, an Applicant is not limited to information within the four corners of the specification when called upon to demonstrate that the written description requirement is satisfied. Applicant respectfully asserts that the claimed invention has been described with sufficient particularity.

The Examiner is requested to note that gram-negative bacterial species that contain an *rfe* gene can be employed in the methods of the invention. The specification discloses the use of *E. coli* K-12, which can be employed in the methods of the invention. Further, as Alexander et al. (discussed herein) observed, the *rfe* gene is present in many different *E. coli* strains, for example, strains O18, O75 and O111. Additionally, Alexander et al. disclose that *rfe* has been shown to be involved in the biosynthesis of O8 and O9 in *E. coli*, and in O1 in *Klebsiella pneumoniae*. Moreover, Dr. Apicella's Declaration, submitted on November 06, 2001, demonstrates that gram-negative bacteria other than *E. coli* can be used to make complex carbohydrates with the *lsg* locus. Specifically, Dr. Apicella demonstrated the feasibility of using *Salmonella minnesota* to make complex carbohydrates with the *lsg* locus. Additionally, the specification discloses at page 4, line 29 through page 5, line 1, that *rfe* from *H. influenzae* may be used. At page 6, lines 6-8, it is disclosed that the nucleotide sequence for a *H. influenzae* *rfe* is available in the TIGR database. Further searching of the TIGR database for *rfe* genes revealed that an *rfe* gene, at the time the application was filed, was known to the art workers in *Aquifex aeolicus*. (Primary Accession Number 066884; Sequence last modified in August, 1998). Moreover, Cole et al. had previously disclosed the sequence of the *rfe* protein from *Mycobacterium tuberculosis* (Cole et al., *Nature*, 393, 537-544 (1998); sequence available, as disclosed in Cole et al., from <http://www.sanger.ac.uk> as Rv1302). Thus, Applicant submits that Applicant's disclosures in the specification as filed with respect to an *rfe* gene, when read in the context of what was known to the art worker, satisfies the written description requirement of 35 U.S.C. § 112, first paragraph.

Applicant also asserts that the issues involved in the instant case are distinguishable from

the issues in the recent case of *Enzo v. Gen-Probe (Enzo Biochem., Inc. v. GenProbe, Inc., 285 F.3d 1013, 62 U.S.P.Q.2d 1289 (Fed. Cir. 2002)*. In *Enzo*, the court ruled that when an application contains claims to nucleic acid sequences, a reference to a source of material from which those sequences could be determined did not satisfy the written description requirement. However, in the instant application, Applicant is claiming methods that involve the use of sequences that were already in the art worker's possession when the application was originally filed. Therefore, Applicant respectfully asserts the specification satisfies the written description requirement of 35 U.S.C. § 112, first paragraph.

Therefore, after considering both the disclosures in the specification, and also the information known to the art worker, Applicant respectfully asserts that the specification does convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was legally in possession of the elements of the invention sought to be patented. Thus, it is submitted that the 35 U.S.C. § 112, first paragraph, written description requirement has been met. Therefore, the Examiner is respectfully urged to withdraw the written description rejection.

B. The Enablement Rejection

The Examiner rejected claims 8, 11-12 and 20-21 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable the production of a lipooligosaccharide (LOS) using a *rfe* gene different from the *E. coli rfe*. The Examiner asserts that it would take undue experimentation for an art worker to produce LOS by the claimed methods using a *rfe* from a source other than *E. coli*. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

To be enabling, the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 42 U.S.P.Q.2d (BNA) 1001, 1004 (Fed. Cir. 1997). The scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *Id.* Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a matter of degree. *PPG Industries Inc. v. Guardian Industries Corp.*, 156 F.3d 1351, 37 U.S.P.Q.2d (BNA) 1618, 1623 (Fed. Cir. 1996). The fact that some experimentation is necessary

does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *Id.*

Applicants assert that the present specification teaches one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The Examiner has conceded that the specification does enable the production of LOS using an *E. coli rfe*. Dr. Apicella's Declaration demonstrates that gram-negative bacteria other than *E. coli* can be used to make complex carbohydrates with the *lsg* locus. Furthermore, as discussed hereinabove, *rfe* genes other than that of *E. coli* were known to the art worker. As the present specification discloses methods to screen products produced by the disclosed methods (Example 6), practitioners in the art related to the present application would be well-equipped to prepare constructs having *rfe* genes other than *E. coli*, and screen such constructs. As the Examiner states at page 6 of the Office Action, recombinant technology is performed routinely in the art. Therefore, the art worker in possession of Applicant's disclosures would be able to make and use the full scope of the claimed invention without undue experimentation.

Applicant therefore asserts that the specification fully enables one skilled in the art to use the method of the present invention. The first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims, and this requirement has been met. It is respectfully submitted that the pending claims conform with 35 U.S.C. § 112, first paragraph. Therefore, Applicant requests that the Examiner withdraw the 35 U.S.C. § 112, first paragraph enablement rejection of the claims.

III. The 35 U.S.C. § 103(a) Rejection of the Claims

The Examiner rejected claims 6-8, 11-12 and 18-21 under 35 U.S.C. § 103(a) as being unpatentable over McLaughlin et al. (*Journal of Endotoxin Research*, 1, 165 (1994)) in view of Alexander et al. (*J. of Bacteriology*, 176, 7079 (1994)). As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

Independent claim 11 recites a process for the production of a *Haemophilus influenzae*-specific lipooligosaccharide (LOS) which comprises the steps of (a) growing in a culture

medium gram-negative bacteria comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence comprising an *rfe* gene, and (iii) an isolated DNA sequence comprising a lipooligosaccharide-synthesis gene (*lsg*) from *Haemophilus influenzae*, wherein the protein encoded by the *rfe* gene is expressed and adds an acceptor molecule to the heptose molecule to synthesize an oligosaccharide; and (b) recovering the *H. influenzae*-specific LOS from the culture medium. Claims 6-8, 12, 18-19 and 22 depend from claim 11.

Independent claim 20 recites a method of modifying a terminal heptose of a lipopolysaccharide (LPS) or lipooligosaccharide (LOS) core structure of a gram-negative bacterial species containing an *rfe* gene comprising regulating the protein encoded by the *rfe* gene with a protein encoded by an isolated *lsgG* gene from *Haemophilus influenzae* in order to catalyze transferring N-acetyl glucosamine onto the terminal heptose.

Independent claim 21 recites a process for the production of a complex carbohydrate comprising the steps of: (a) growing in a culture medium gram-negative bacteria comprising (i) a core lipid structure containing a terminal heptose and (ii) a DNA sequence comprising an *rfe* gene, and (iii) an isolated DNA sequence comprising a liposaccharide-synthesis gene G (*lsgG*) from *Haemophilus influenzae*, wherein the protein encoded by the *rfe* gene is expressed and adds an acceptor molecule to the heptose molecule to synthesize complex carbohydrate; and (b) recovering the complex carbohydrate from the culture medium.

To establish a *prima facie* case of obviousness, the Examiner has the burden to establish three basic elements. First, the Examiner must establish that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the Examiner must establish that there is a reasonable expectation of success. Finally, the Examiner must establish that the prior art reference teaches or suggests all the claim limitations (M.P.E.P. § 2143).

Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness because the art does not provide a suggestion or motivation to combine the documents. Applicant also asserts that the Examiner has applied inappropriate hindsight. Finally, Applicant asserts that, even if combined, the cited documents fail to teach or suggest all

of the elements of Applicant's claimed invention.

Applicant respectfully submits that the art does not provide a suggestion or motivation for combining the cited documents.

The teaching or suggestion to arrive at the claimed method, and the reasonable expectation of success, must both be found in the prior art, not in Applicant's disclosure (M.P.E.P. § 2143 citing with favor, *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)). The Examiner must provide specific, objective evidence of record for a finding of a suggestion or motivation to combine the reference teachings and must explain the reasoning by which the evidence is deemed to support such a finding. *In re Sang Su Lee*, 277 F.3d 1338, 61 U.S.P.Q.2D 1430 (Fed. Cir. 2002). Mere conclusory statements do not fulfill the Examiner's burden. *Id.* As has been clearly stated, (*Id.* at 1433)

[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. *See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (*quoting C.R. Bard, Inc., v. M3 Systems, Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998)); *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) ("teachings of references can be combined only if there is some suggestion or incentive to do so.") (emphasis in original) (*quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)).

Applicant respectfully submits that the Examiner has not provided such evidence or explanation for a suggestion or motivation to combine the cited documents. Instead, the Examiner merely attempted to characterize Alexander et al. and McLaughlin et al. and then made the conclusory statement: "Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make lipooligosaccharides with *E. coli* K-

12 expressing an *E. coli rfe* and an *H. influenzae lsg*." The Examiner follows that statement with: "The motivation of making *H. influenzae*-specific lipooligosaccharides is to produce the lipooligosaccharides in large amounts to effectively obtain oligosaccharides, useful in developing vaccines and in identification of *H. influenzae* bacteria itself." These statements appear to be relate to independent claim 11, which is directed to a process for the production of a *Haemophilus influenzae*-specific lipooligosaccharide. The Examiner does not explain why a process of modifying the terminal heptose of a LPS or LOS core structure of a gram-negative bacteria (independent claim 20) or why a process for the production of a complex carbohydrate (independent claim 21), are unpatentable over the cited documents.

It is respectfully submitted that the Examiner is employing hindsight to arrive at Applicant's invention in the absence of any suggestion in the cited art to take Applicant's approach. The Examiner is reminded that it is impermissible to use Applicant's specification as a template to arrive at the conclusion that the claimed invention is obvious. *In re Fritsch*, 23 U.S.P.Q.2d 1780, 1782 (Fed. Cir. 1992). To render an invention obvious, the combination of the cited art must teach or suggest the claimed invention and provide a reasonable expectation of success in preparing the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Applicant respectfully submits that the cited art does not provide a suggestion or motivation to combine Alexander et al. with McLaughlin et al. Furthermore, even if combined, the cited documents fail to teach or suggest all of the elements of Applicant's claimed invention.

Alexander et al. disclose that the *rfe* gene is important in the first step in the biosynthesis of the O7 repeating unit of lipopolysaccharide (LPS) in *E. coli*. and suggest that the *rfe* gene may have a general role in the biosynthesis of O-specific polysaccharides (page 7079, second column, first full paragraph). Alexander et al. also disclose that the *rfe* gene is present in different *E. coli* strains, for example, strains O18, O75 and O111 (page 7082, first column, first full paragraph). Furthermore, while acknowledging that the role of *rfe* is not clearly understood in these cases, Alexander et al. disclose that *rfe* has been shown to be involved in the biosynthesis of O8 and O9 in *E. coli*, and in O1 in *Klebsiella pneumoniae*. (page 7083, column 1, fourth full paragraph)

Alexander et al. do not suggest teach or suggest a process of making lipooligosaccharides (claim

11) or complex carbohydrates (claim 21) in gram-negative bacteria which include a DNA sequence comprising an *rfe* gene and an isolated DNA sequence comprising an *lsg* from *Haemophilus influenzae*. Nor does Alexander et al. teach or suggest a method of modifying a terminal heptose of a lipopolysaccharide (LPS) or LOS by regulating a protein encoded by *rfe* with a protein encoded by *lsgG* from *Haemophilus influenzae* (claim 20). Alexander et al. does not even mention *lsgG*.

McLaughlin et al. is directed to the characterization and sequence analysis of the lipooligosaccharide (LOS) synthesis genes (*lsg*) locus from *Haemophilus influenzae* type b. McLaughlin et al. teach that the complexity of *Haemophilus influenzae* LOS “has made the analysis of the terminal LOS sugars difficult and has hindered assignment of specificities to the biosynthesis genes involved in their production (page 166, column 1). McLaughlin et al. disclose that the *lsg* sequenced had a length of 7435 bp that encompasses 7 complete and 1 partial open reading frames (ORFs 1-8) (page 167, first paragraph of RESULTS). However, “it was not possible to deduce functions of the products of the ORFs based on sequence homology (page 172, first paragraph of the DISCUSSION).” As the Examiner acknowledges at page 6 of the Office Action, “McLaughlin et al. does not teach a process of making the lipooligosaccharide using a *rfe* enzyme.” Nor does McLaughlin et al. does not teach or suggest a process of making complex carbohydrates using *rfe* or teach or suggest a method of modifying a terminal heptose of a lipopolysaccharide (LPS) or LOS by regulating a protein encoded by *rfe* with a protein encoded by *lsgG*. McLaughlin et al. does not even mention *lsgG*.

Thus, even when combined, these references do not meet all three requirements for *prima facie* obviousness. Furthermore, neither Alexander et al. or McLaughlin et al., either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

D. Conclusion

For the reasons described hereinabove, Applicant submits that the Examiner has not make out a *prima facie* case of obviousness because the art does not provide a suggestion or motivation to combine the documents. Applicant also asserts that the Examiner has applied inappropriate hindsight. Finally, Applicant asserts that, even if combined, the cited documents fail to teach or

suggest all of the elements of Applicant's claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION


Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Box AF, Commissioner of Patents, Washington, D.C. 20231, on this 15th day of July, 2002.

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Name


Signature